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①⑨ (CA) **CANADIAN PATENT** ⑫

⑤④ SKELETAL IMAGING KIT UTILIZING TRIETHYLENE  
TETRAMINE HEXA (METHYLENE PHOSPHONIC ACID)

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12 BACKGROUND OF THE INVENTION

13 Various 99m Technetium labeled phosphate compounds  
14 have been tested for their use as bone imaging agents using  
15 a variety of radiographic bone scanning techniques. In  
16 general, the prior art methods prepared bone imaging agents  
17 by mixing a solution of Technetium-99m as the pertechnate  
18 with a freeze-dried mixture of a phosphate or a phosphonate  
19 compound and stannous chloride employed as the reducing or  
20 complexing agent. These prior art methods are referred to  
21 in detail in RADIOPHARMACEUTICALS, edited by Subramanian,  
22 Rhodes, Cooper, and Sodd, 1975, particularly in the chapter  
23 entitled, "An Evaluation of 99m TC Labeled Phosphate Com-  
24 pounds as Bone Imaging Agents" pp. 319-328 inclusive. This  
25 reference indicates that 99m TC labeled methylene diphos-  
26 phonate is the agent of choice for bone imaging in nuclear  
27 medicine.



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1 More recently, additional phosphonate compounds  
2 have been tested as both skeletal and myocardial infarct  
3 agents--JOURNAL OF NUCLEAR MEDICINE, June 1975, p. 540.  
4 Here there is described the use of various ethylene diamine  
5 polyphosphonic acid and, in particular, diethylene triamine  
6 penta (methylene phosphonic acid). The particular phos-  
7 phonates mentioned are reported to be likely candidates  
8 for clinical use in view of the fact that they are cleared  
9 from the blood more rapidly than the agents utilized in  
10 the past.

11 SUMMARY OF THE PRESENT INVENTION

12 In accordance with the present invention, there  
13 is provided a diagnostic kit suitable for use in radio-  
14 graphic scanning of bone. The kit ordinarily contains  
15 sufficient material for more than one dose. It comprises  
16 a freeze-dried mixture of the components suitable for re-  
17 constitution with a solution of sodium pertechnate. The  
18 present kit employs a single container including a re-  
19 ducing agent and an organic compound for use in the prep-  
20 aration of an injectable bone imaging diagnostic kit. The  
21 kit comprises a freeze-dried mixture of a water-soluble salt  
22 of triethylene tetramine hexa (methylene phosphonic acid)  
23 and a non-toxic stannous salt.

24 This diagnostic kit preferably comprises a freeze-  
25 dried mixture of approximately 10 mg. of the triethylene  
26 tetramine hexa (methylene phosphonic acid) (TTHMP) and  
27 250 mcg. of stannous chloride as the dihydrate. Although  
28 this ratio is preferred, the stannous chloride compound is  
29 effective in amounts of from 1-100 mg. of stannous chloride  
30 dihydrate mixed with 10 mg. of TTHMP.

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1       The TTHMP used as the phosphonate component of  
2 the kit is prepared in the following manner. An aqueous  
3 solution of triethylene tetramine is treated with excess  
4 dilute hydrochloric acid to produce the tetrahydrochloride  
5 salt. This aqueous solution of salt is then added to a  
6 mixture of 6 moles of phosphorus trichloride in dilute  
7 hydrochloric acid and refluxed for a period of about one  
8 hour while adding 12 moles of formaldehyde in dropwise  
9 fashion as a 37% aqueous solution and refluxed for an  
10 additional one hour to produce the desired compound--TTHMP.  
11 The reaction mixture containing the desired product is  
12 adjusted to pH 6 with dilute sodium hydroxide and heated  
13 to the boiling point. To the boiling solution of the free  
14 acid is then added an aqueous solution of 6 moles of lead  
15 II nitrate, which furnishes a voluminous precipitate of  
16 the lead salt of the acid. The lead salt is recovered by  
17 filtration and washed with hot water. In order to remove  
18 the lead and recover the free acid, the lead salt is sus-  
19 pended in water, and hydrogen sulfide gas is bubbled through  
20 the solution to precipitate the lead as the sulfide and  
21 leave the TTHMP free acid in solution. The suspension of  
22 lead sulfide is removed by filtration, yielding the TTHMP  
23 free acid in solution in the filtrate. The aqueous fil-  
24 trate is then reduced in volume by concentration under  
25 reduced pressure to the consistency of a thick syrup. The  
26 free acid is precipitated from the syrup by the addition  
27 of 10 volumes of ethanol. The aqueous ethanol suspension  
28 of the free acid is then concentrated under reduced pres-  
29 sure, leaving a yield of dry residue of precipitated TTHMP  
30 free acid, which is pulverized to a powder suitable for  
31 use in preparation of the kit.

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1           In the process of preparing the instant diagnostic  
2 kit, it is essential that the single vial be prepared ob-  
3 serving aseptic techniques and using normal saline solution  
4 as the diluent so that the ingredients, when reconstituted  
5 with Technetium 99m, are compatible with body fluid and may  
6 be intravenously injected without further treatment after  
7 mixing. Another important feature of the present invention  
8 is the ratio of amounts of the TTHMP and the stannous salt  
9 employed as the complexing agent. It is important to the  
10 present invention that the weight ratio of TTHMP to stannous  
11 salt is about 40:1. In preparing the components of the  
12 present kit, the first component is prepared by dissolving  
13 40 parts by weight of TTHMP and 1 part by weight of stannous  
14 chloride dihydrate in water made slightly acid (pH 3-5)  
15 with hydrochloric acid and diluting with water to a con-  
16 centration of approximately 5 mgm./ml. of TTHMP by weight,  
17 subdividing the bulk solution into individual dosage amounts  
18 and aseptically freeze drying the individual dosages to  
19 provide a readily-soluble mixture of 10 mg. TTHMP and 250  
20 mcg. stannous chloride as the dihydrate.

21           The kit comprising the freeze-dried mixture of  
22 TTHMP and stannous chloride is readily employed as a diag-  
23 nostic tool for skeletal imaging in the following manner.  
24 To the freeze-dried mixture of TTHMP and stannous chloride  
25 is added a solution of 2-8 ml. of a solution containing  
26 approximately 20-100 millicuries of sodium pertechnetate Tc  
27 99m. The resulting injectable solution of TTHMP-stannous  
28 complex labeled with Tc 99m can be used immediately without  
29 further treatment.

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1           In utilizing the instant kit for skeletal imaging,  
2 an aqueous solution of from 2-3 millilitres of the required  
3 amount of sodium pertechnetate Tc 99m (available as instant  
4 Technetium 99m or from a sterile generator of the type  
5 described in U.S. Patent 3,369,121) is mixed with the lyo-  
6 philized mixture of TTHMP and stannous chloride to form a  
7 solution of reduced pertechnetate ion bound to the phospho-  
8 nate compound, which solution is immediately ready for  
9 injection into the patient. Intravenous injection of  
10 approximately 10 millicuries of the Tc 99m TTHMP-stannous  
11 complex is followed by imaging of the animal skeleton in  
12 approximately 1-2 hours. The present kit is highly satis-  
13 factory because of its simplicity and is readily employed  
14 by the clinician with maximum economy of time and effort.

EXAMPLE 1

Preparation of Kit Containing a Freeze-Dried Mixture of 10 Mg. of Triethylene tetramine hexa (methylene phosphonic acid) and 250 mcg. Stannous Chloride dihydrate

The solution is subdivided into 2 ml. portions and filled into 10 ml. vials. The subdivided solutions are then aseptically freeze-dried to provide a readily-soluble, freeze-dried mixture of 10 mg. TTHMP and 250 mcg. stannous chloride dihydrate in each vial and stored in a nitrogen atmosphere.

17 EXAMPLE 2

18 Use of Kit in Preparing Injectable Bone Imaging Solution

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A kit for the preparation of an injectable solution incorporating Technetium 99m which comprises in a single sterile container a freeze-dried mixture of triethylene tetramine hexa (methylene phosphonic acid) or a water-soluble salt thereof and a water-soluble tin salt.
2. A kit for the preparation of an injectable solution incorporating Technetium 99m which comprises in a single sterile container a freeze-dried mixture of triethylene tetramine hexa (methylene phosphonic acid) or a water-soluble salt thereof and a water-soluble tin salt in a ratio by weight of from 10-100 parts of triethylene tetramine hexa (methylene phosphonic acid) and 1 part of tin as stannous chloride-dihydrate.
3. A kit in accordance with Claim 2 in which the weight ratio of the components is 40 parts of triethylene tetramine hexa (methylene phosphonic acid) and 1 part of tin as stannous chloride-dihydrate.
4. A kit in accordance with Claim 3 in which the triethylene tetramine hexa (methylene phosphonic acid) is present as the free acid and the tin is added in the form of stannous chloride-dihydrate.

